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(54) Title: METHOD OF NEUTRALIZING STRESS SEQUELAE AND OF REDUCING THE INCIDENCE OF SCOURS IN MONOGASTRIC ANIMALS AND RUMINANTS, AND A FEED ADDITIVE OF STRESS-COUNTERACTING, DIARRHOEA-COUNTERACTING AND GROWTH-PROMOTING ACTIVITY

(57) Abstract

Stress and diarrhoea sequelae in monogastric animals and ruminants can be prevented or treated by mixing the animal feed with an effective amount of a additive based on a Plantago species, preferably Ispaghula Husk, in the form of seed hull, ground seeds or extract of seeds. The remedy is administered in an amount of about 0.3 weight percent, when used as a preventive, and in an amount of about 0.5 g per kg of body weight, when the diarrhoea and/or stress state is observed. The remedy further has growth-promoting activity.

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Method of neutralizing stress sequelae and of reducing the incidence of scours in monogastric animals and ruminants, and a feed additive of stress-counteracting, diarrhoea-counteracting and growth-promoting activity.

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The present invention concerns a method of neutralizing stress sequelae and of reducing the incidence of scours in monogastric animals, poultry and ruminants. The 10 invention further concerns a feed additive which is useful for this purpose and also has a growth-promoting effect.

The incidence of diarrhoea particularly in newborn and 15 quite young domestic animals is a considerable problem with tremendous economic consequences for the farmer. Especially in the breeding of pigs is this a very pronounced problem. Newborn pigs usually remain with the sow for ~~some~~ weeks and are then taken from the sow, 20 placed in community pens and fed a dry feed. The weaning creates stress and often 50 percent of the pigs develops scours within 2-3 days after being taken from the sow. Of the pigs which develop scours, it is not unusual for one-fifth to die, while another three-fifths will lose 25 a significant amount of weight through rapid dehydration. Only about 20 percent of the pigs with scours will recover without an appreciable loss of weight.

Also newborn calves suffer severely from diarrhoea, which 30 is far and away the most important cause of death of newborn cattle in the dairy industry. The frequent incidence of scours in newborn calves is a source of considerable expenses and difficulties in the dairy industry, and thus a great need exists for finding new 35 means and ways of preventing and curing scours in animals.

These incidences of scours can, as mentioned, be related to stress in animals. The animals can also be thrown into a state of stress during transport and immediately before 5
slaughter, which causes a considerable dehydration of the cells to the gastro-intestinal tract with a consequent loss both in live and slaughtered weight.

Crowding of many young animals per unit of area often causes the micro-flora to be activated, which forms a 10
constant threat to the animals' health.

Diarrhoea is generally a manifestation of a more or less pathogenic micro-flora, and reactions from the intestinal canal in the form of diarrhoea is the result of water 15
balance changes. Diarrhoea can have different causes, such as hormonal changes in the mother's milk or a high content of incorporated carbohydrates in the feed.

Stress can also develop under the influence of heat and 20
by shortage in the liquid supply.

It has now surprisingly been found that *Plantago* species in the form of seed husk, whole or ground seeds or extractions thereof, used as an additive to animal feeds, gives an extremely favourable result in preventing 25
stress states of the above mentioned type, and/or in preventing or treating scours, and/or in obtaining a growth-promoting effect, especially in monogastric animals, such as pigs, horses, minks, dogs, cats and 30
other pets, as well as poultry, but also in ruminants, such as calves and sheep both at the stage when they only have one active stomach (e.g. calves and lambs) and when they are full-grown (e.g. cows and sheep).

35 Plantago seeds are widely used as a human laxative in various dosage-forms and has for centuries been used as

a remedy against a large number of human diseases, such as inflammation of the eye, dry coughs, burns and certain gastric and intestinal disorders (see e.g. Martindale, The Extra Pharmacopoeia 26th ed., p. 1084 and 5 J.N. BeMiller: Natural Gums, chapter XVI, p. 345-354).

The effect of Plantago seeds is due to the content of gum, which can be readily extracted with hot water. It is, however, not necessary to extract the gum since the 10 seeds can in ground form be used directly because of their great mucilage-forming capacity.

To the best of the applicant's knowledge Plantago species have never been tried to control serious 15 scours in animals, nor to neutralize stress states, but it has now been found that the use of Plantago in animals gives several significant benefits in that respect.

A preferred Plantago product is Ispaghula (BPC) because 20 this has the highest content of polysaccharide. Ispaghula consists of the dried, ripe seeds of Plantago ovata Forskal. In the USA the designation "Psyllium seeds" covers both Plantago ovata, P. indica and P. psyllium seeds. In Denmark the name "loppefrø" (fleasheeds) only 25 covers P. psyllium and P. indica. The main constituents of Ispaghula are polysaccharides (about 30%), composed of D-xylose, L-arabinose, L-rhamnose and D-galacturonic acid. Ispaghula Husk is the name of epidermis and collapsed adjacent layers removed from Ispaghula.

30 The polysaccharide content is higher than in Ispaghula. Therefore and because the outer seed embryo contains a pigment that causes a brown coloration of the kidneys, the use of Ispaghula Husk is preferred to the whole seeds.

35 Among the physical properties of Ispaghula Husk, the most

remarkable one is its ability to absorb water under formation of a highly viscous mucilage. A dispersion of 1 percent Ispaghula Husk in water gives a viscosity of 4000 cP. The dispersions are thixotropic. The viscosity 5 is only slightly affected by temperature variations between 20 and 50°C, pH variations between 2 and 10 and electrolyte solutions up to 0.2 M (sodium and potassium chloride).

10 Ispaghula Husk, when ingested by animals with the proper amount of water, swells and becomes an integral part of the fecal mass. Ingestion of 8 g of Ispaghula Husk is able to increase the fecal mass by more than 200 ml owing to the water bound.

15 Ispaghula Husk has no nutritional value and is not broken down during the passage through the intestinal tract of the animal. The substance binds toxines and allergens.

20 Ispaghula Husk has a plurality of advantages which make the substance useful for prevention and treatment of animal scours:

25 - it is a safe and harmless natural product which is widely used in humans,

- it does not alter the normal bacterial flora, either in the intestines or in the excrements,

30 - it does not change iron and calcium resorption,

- it is heat resistant and is not broken down in boiling water, thus it can be easily formulated as pellets; in 35 this context it acts as a binder and prevents dust formation,

- its properties do not change by the addition of NaCl or KCl, even in the presence of citric acid (this is essential in the treatment of severe diarrhoea, where such treatment is given with potassium ions),

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- the treatment is simple and inexpensive and requires no veterinary assistance, and

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- because of its great waterbinding capacity, it exerts a hydrostatic effect on the water balance between the intestine and the surrounding cells, counteracting the liberation of water from the cells in consequence of stress.

15 The recommended dose is low: To prevent the sequelae of the water and salt loss caused by stress and diarrhoea the dose normally used is of the order 0.3 % mixed with the animal feed, independent of the species of animals treated, but also smaller additions, such as 0.2 % are
20 efficacious. For curative treatment of the sequelae the dose normally used is of the order 0.5 g per kg of body weight. The dose is, however, not critical; large doses are well tolerated. To prevent stress during transport and before slaughtering, doses corresponding to the
25 curative treatment or larger can advantageously be administered about 24 hours ahead.

The preferred product for the purpose of the invention has, as mentioned, its origin in the *Plantago ovata* species,
30 but even products originating in other *Plantago* species, such as *P. psyllium*, *P. indica*, *P. lanceolata* and *P. major*, can be used with similarly good results.

35 The following examples illustrate more closely the effect obtained by using the preferred product, Ispaghula Husk.

Example 1

Tests performed with Ispaghula Husk mixed into feeds for piglets.

5

The effect of Ispaghula Husk on piglets suffering from chronic scouring and dehydration in the phase of weaning was tested in the following way:

10 16 piglets weighing from 15 to 20 kg, were separated in two groups according to weight and clinical symptoms. The two groups were placed in their respective pens.

15 8 piglets received 6-8 g of Ispaghula Husk daily for 14 days, the substance being mixed into the feed. The pigs received no additional antibiotic treatment.

20 The incidence of scours decreased successively within 4-5 days, and the fecal consistency improved practically to normal. One of the piglets died 5 days after the treatment was commenced.

25 The 8 piglets in the control group received no treatment. Four of these piglets died during the test period from continued scours and dehydration.

Test with 5-10 week old pigs showed that an admixture of 0.3 percent Ispaghula Husk in the feed, corresponding with 0.3 to 3 g a day per pig, had a stabilizing effect on the 30 fecal consistency, reducing the incidence of scouring remarkably, especially in pigs which were weaned at the age of 8 weeks.

Example 2

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A test with 20 day old weanlings was carried out. The

piglets were placed in steelpens and separated in two groups: Control (C) and Test (T) with 40 piglets in each. The average weight in each group was five kg. Feed and water were available on a free choice basis.

5

The control group was given a standard feed for weanlings. The test group was given Ispaghula Husk mixed with a standard feed for weanlings in the ratio of 3 kg Ispaghula Husk to 1000 kg standard feed.

10

The total incidence of scours was designated S. The watery scours were designated WS. The average feed consumption F and the average growth G for each group during the first three weeks and the following two weeks of the 15 test period were recorded.

Test results

The incidence of scours (weekly average per 1000 animals) 20 appears from table I.

Table I

	Week	T-S	T-WS	C-S	C-WS
25	1	65	19	89	19
	2 and 3	155	72	254	149
	4 and 5	94	30	107	29

During the first week there were no significant differences 30 between the two groups, the incidence of scours being low everywhere.

During the second week S / WS increased rapidly in the C group to a maximum of 260 / 155.

35

During the third week the two groups remained at the same

level as in the previous week.

During the fourth week S/WS declined rapidly to 105/28 in the C group, whereas it took the T group two days 5 more to arrive at 90/25.

The levels remained unchanged in the fifth week.

Table II

10

Average feed consumption and growth in the test period:

Week	T-F	T-G	C-F	C-G
0-3	7.27	5.75	7.14	5.53
15 4-5	10.75	7.48	10.57	7.03

Table III

Feed consumption to obtain a growth of 1 kg:

20

Week	T $\frac{F}{G}$	C $\frac{F}{G}$
0-3	1.264	1.290
4-5	1.432	1.504

25

Table IV

Difference in the feed consumption per 1 kg growth between the 2 groups:

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Week	$\frac{I}{C}$
0-3	0.98
4-5	0.95

35 The effect of Ispaghula Husk admixture to the feed can - in cases where no drastic diarrhoea occurs - be measured

best from the amount of feed necessary to obtain a growth of 1 kg. As appears from the above figures, the test animals used 2 percent less feed during the first three weeks and 5 percent less feed during the weeks 4 and 5 than the control animals.

Patent Claims

1. A method of neutralizing stress sequelae and of reducing
5 the incidence of scours in monogastric animals, poultry
and ruminants, characterized by administering
to the animal an effective amount of a feed additive based
on a *Plantago* species.
- 10 2. A method according to claim 1, characterized
by the fact that the *Plantago* species employed is *P. ovata*,
P. psyllium, *P. indica*, *P. lanceolata* or *P. major*.
- 15 3. A method according to claim 1 or 2, characterized
by the fact that the product employed is
Ispaghula, preferably *Ispaghula Husk*.
- 20 4. A method according to claim 1, 2 or 3, characterized
by the fact that the animal is fed a feed
containing about 0.3 percent by weight of *Ispaghula Husk*.
- 25 5. A method according to claim 1, 2 or 3, characterized
by the fact that the animal is fed a feed
containing *Ispaghula Husk* equivalent to 0.5 g per kg
of body weight.
- 30 6. A feed additive of stress-counteracting, diarrhoea-
counteracting and growth-promoting activity, characterized
by the fact that it is based on seeds
from plants of a *Plantago* species.
- 35 7. A feed additive according to claim 6, characterized
by the fact that the *Plantago* species employed
is *P. ovata*, *P. psyllium*, *P. indica*, *P. lanceolata* or
P. major.

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8. A feed additive according to claims 6 and 7,
characterized by the fact that it consists
of seeds, seed hulls or extracts of seeds of the selected
Plantago species.

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9. A remedy according to claims 6-8, characterized
by the fact that it contains Ispaghula in the
form of Ispaghula Husk.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/DK82/00013

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

A 23 K 1/14, A 61 K 35/78

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC 3	A 23 K 1/00, 1/14, 1/18, A 61 K 35/78, C 08 B 37/00, C 08 L 5/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT **

Category *	Citation of Document, * with indication, where appropriate, of the relevant passages **	Relevant to Claim No. 13
A	US, A, 4 120 952 (ARIZONA FEEDS) 17 October 1978, see column 7, claim 1	6
A	US, A, 2 060 336 (LIBBY, McNEILL & LIBBY) 10 November 1936, see page 1, left column, lines 23-33 and right column, lines 3-8	6
A	FR, A, 1 461 547 (CHARLES MARIE GEORGES KUNTZ) 9 December 1966, see page 2	6
L	Remington's Pharmaceutical Sciences, 15th ed. 1975, see page 714, 746 (MACK PUBLISHING Co)	6
A	The Extra Pharmacopoeia, 26th ed. (1972), see page 1084 (W MARTINDALE)	6
A	Natural Gums, Chap. XIV, see page 345-354, (spec. 350-351) (J N BeMILLER)	6

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IV. CERTIFICATION

Date of the Actual Completion of the International Search:

1982-04-19

Date of Mailing of the International Search Report:

82-36-25

International Searching Authority:

Swedish Patent Office

Signature of Authorized Officer **

Inga-Karin Petersson
Inga-Karin Petersson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields Searched (cont)

US CI 424:35, 180, 195, 355, 361;
426:69, 74, 518, 623, 625, 630,
635, 636, 658

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹³

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers ..1-5, because they relate to subject matter ¹³ not required to be searched by this Authority, namely:

Methods for treatment of the animal body by therapy.

2. Claim numbers , because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out ¹³, specifically:

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹³

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.

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